PATENT COOPERATION ATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 30 March 2000 (30.03.00)	
International application No. PCT/EP99/05459	**Applicant's or agent's file reference** 1634PTWO
International filing date (day/month/year) 30 July 1999 (30.07.99)	**Priority date** (day/month/year) 05 August 1998 (05.08.98)
Applicant ALTAMURA, Maria et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

29 February 2000 (29.02.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Claudio Borton
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
1634PTWO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 05459	30/07/1999	05/08/1998
Applicant		
MENARINI RICERCHE S.P.A. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/05459

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/023 A61K38/07 C07K7/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 34949 A (BUGNO CRISTINA DI ;MAGGI CARLO ALBERTO (IT); MENARINI RICERCHE S P) 13 August 1998 (1998-08-13) cited in the application the whole document	1-3, 12-19
A	KUCHARCZYK N ET AL: "TETRAPEPTIDE TACHYKININ ANTAGONISTS: SYNTHESIS AND MODULATION OF THE PHYSICOCHEMICAL AND PHARMACOLOGICAL PROPERTIES OF A NEW SERIES OF PARTIALLY CYCLIC ANALOGS" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 36, no. 11, page 1654-1661 XP000197372 ISSN: 0022-2623	

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 1999	22/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cervigni, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/05459

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 703 034 A (FREIDINGER ROGER ET AL) 27 October 1987 (1987-10-27)	
A	WO 93 03059 A (MENARINI FARMA IND) 18 February 1993 (1993-02-18)	
A	MCKNIGHT A T ET AL: "PHARMACOLOGICAL SPECIFICITY OF NOVEL, SYNTHETIC, CYCLIC PEPTIDES AS ANTAGONISTS AT TACHYKININ RECEPTORS" BRITISH JOURNAL OF PHARMACOLOGY,GB,BASINGSTOKE, HANTS, vol. 104, no. 2, page 355-360 XP002036785 ISSN: 0007-1188 cited in the application	
A	EP 0 528 312 A (TAKEDA CHEMICAL INDUSTRIES LTD) 24 February 1993 (1993-02-24)	
A	WO 96 28467 A (MENARINI FARMA IND ;ARCAMONE FEDERICO (IT); MAGGI CARLO ALBERTO (I) 19 September 1996 (1996-09-19)	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/05459

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9834949	A	13-08-1998	IT	FI970020 A	07-08-1998
			AU	6620198 A	26-08-1998
			ZA	9800931 A	07-08-1998
US 4703034	A	27-10-1987	NONE		
WO 9303059	A	18-02-1993	IT	1258939 B	08-03-1996
			IT	1251164 B	04-05-1995
			AU	2387592 A	02-03-1993
			EP	0606222 A	20-07-1994
			JP	6509571 T	27-10-1994
			PT	100764 A	28-02-1994
EP 0528312	A	24-02-1993	AT	155486 T	15-08-1997
			CA	2075878 A	14-02-1993
			DE	69220861 D	21-08-1997
			DE	69220861 T	20-11-1997
			DK	528312 T	29-12-1997
			EP	0552417 A	28-07-1993
			ES	2103857 T	01-10-1997
			ES	2133295 T	16-09-1999
			FI	923619 A	14-02-1993
			GR	3024495 T	28-11-1997
			JP	2677489 B	17-11-1997
			JP	6009689 A	18-01-1994
			JP	2726647 B	11-03-1998
			JP	8225595 A	03-09-1996
			NO	923142 A	15-02-1993
			US	5616684 A	01-04-1997
			US	5883075 A	16-03-1999
WO 9628467	A	19-09-1996	IT	FI950044 A	13-09-1996
			AU	696528 B	10-09-1998
			AU	5105996 A	02-10-1996
			BG	101849 A	30-04-1998
			BR	9607348 A	30-12-1997
			CA	2215372 A	19-09-1996
			CN	1183786 A	03-06-1998
			CZ	9702862 A	18-02-1998
			EP	0815126 A	07-01-1998
			HR	960117 A	31-08-1997
			HU	9801835 A	28-01-1999
			JP	11501643 T	09-02-1999
			NO	974057 A	07-11-1997
			NZ	303982 A	27-04-1998
			PL	322105 A	05-01-1998
			SK	121297 A	04-02-1998

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1634PTWO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/05459	30/07/1999	05/08/1998
International Patent Classification (IPC) or national classification and IPC C07K5/023		
Applicant MENARINI RICERCHE S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Auth rity and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which hav been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 21 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29/02/2000	31.10.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Korsner, S-E Telephone No. +49 89 2399 8554

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/05459

I. Basis f th r p rt

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

3,6,8,12-19,21-29, 31-35,37	as originally filed			
1,1a,2,2a,4,5,7, 9-11,20,30,36	as received on	13/07/2000	with letter of	11/07/2000

Claims, No.:

1-19	as received on	13/07/2000	with letter of	11/07/2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b))

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-19
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-15, (16-19); see VIII:7 for Claims 16-19
	No:	Claims	

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
s e separate sheet

V. Reasoned statement

The following document will be referred to in this report:

D1 = WO - A - 98/34949

Initial notes:

I.
The present invention focuses on the substituent R4, and the test results on page 37 indicate that the specifically disclosed compounds are generally more active than those of D1.

It should be noted that D1 is no prior art under Rule 64 PCT, but the document will count as an Article 54(3)-document in a later European phase. The international filing date of D1 is 04.02.98, i.e. before the claimed priority date, and the document is therefore valid under Article 54(3) as published, i.e. independent of its priority document, if some formal conditions are fulfilled.
The disclosure of an Article 54(3)-document should be assessed with due regard to the teaching and is not restricted to specific compounds.
It is considered that a small overlap is possible (compare e.g. the definition of NR9R10 in D1 for the case where L=a bond, Q=NR9R10 and R9 & R10 are joined together; see also Example 37 of D1).
This matter has to be settled in a later phase.

II.
The content of the international application has been somewhat broadened over that of the priority document; see i.a. the definitions of R4 and some of the specific compounds.

D1, which was published in August 1998, is therefore normal prior art vis-à-vis the subject-matter added in the international application.

A further consequence of the broadening is that a non-unity problem may arise later; the added alternative definitions of R4 can be seen as different lines of development over known prior art (D1).
This matter should also be settled in a later phase according to national/regional regulations.

1. Novelty (Article 33(2) PCT)

No objection under Rule 64 PCT; the claimed compounds and compositions are novel over the prior art.

2. Inventive step (Article 33(3) PCT)

No objection under Rule 64 PCT; it is considered that the particular definitions of R4 could not have been derived from D1 (concerning the added subject-matter) or any other prior art.

VIII. Certain observations

Reference is made to the claims, but the following inconsistencies (etc.) are also present in the corresponding part of the Description, which should be amended as appropriate.

1.
The formula of original Claim 1 has been redrafted in order to improve the overview.

However, the former definitions of R1, R2, R3 still remain in the text of the Claims. It is only necessary to define "r", Ar and Ar1; see also Claim 2.

2.
It is unclear whether the definitions of haloalkyl (in Ar, Ar1 / Claim 1) refer to C1-3 haloalkyl.

3.
The definitions of R4 should preferably be clarified on page 39; compare lines 3, 15 and 22.

4.
The definition of R4 in Claim 2 is superfluous [already implicit by claim dependency].

5.
Claim 3 could be simplified with regard to " CONR, R is H" -> CONH.
Furthermore, the definitions of f, m and R4 are implicit.

6.
See the implicit definitions of Claims 4, 6, 8, and 10.

7.
Claims 16-19 cover a medical treatment (Rule 67.1(iv) PCT) and are not acceptable under all national/regional regulations.
In case of a later European phase, see Article 52(4) EPC and the Guidelines, C-IV, 4.2.

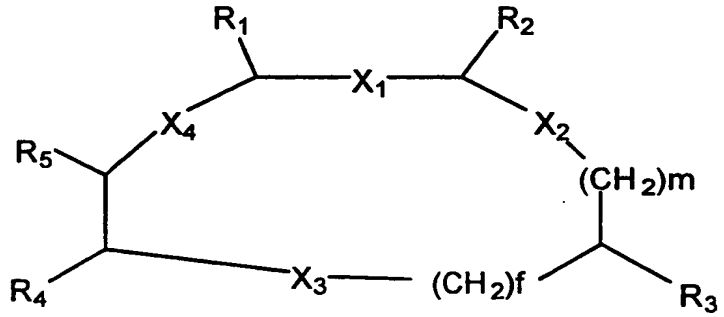
Finally,
D1, being prior art for the added subject-matter, should be identified in the Description (possibly with a note about the circumstances); Rule 5.1(a)(ii) PCT.

- - - - -

MONOCYCLIC COMPOUNDS HAVING NK-2 ANTAGONIST ACTION AND COMPOSITIONS CONTAINING THEM.

Field of the invention

The present invention refers to compound of general formula (I)



(I)

wherein:

X_1, X_2, X_3, X_4, same or different, are a group chosen among: -CONR-, -NRCO-, $-CH_2$-NR-, -NR-CH_2- where R is H , C_{1-3} alkyl, benzyl;

f, m, same or different, are a number chosen among 0,1 and 2;

R_1 and R_2, same or different, are a group:

$-(CH_2)_r$ -Ar where r = 0, 1, 2 and Ar is an aromatic group chosen among: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, benzoimidazole, possibly substituted with up to 2 substituents chosen among C_{1-3} alkyl, haloalkyl, C_{1-3} alkyloxy, C_{2-4} amino-alkyloxy, halogens, OH, NH_2, CN, NR_6R_7, where R_6 ed R_7, same or different, are H or C_{1-3} alkyl,

R_3 is a group chosen among the following groups:

- $(CH_2)_r$-Ar_1 where r = 0, 1, 2 and Ar_1 is an aromatic group chosen among: benzene, naphtalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, benzoimidazole, possibly substituted with up to 2 groups chosen among: C_{1-3} alkyl and haloalkyl, C_{1-3} alkyloxy and amino-alkyoxy, halogens, OH, NH_2, NR_6R_7, where R_6 and R_7, same or different, are H or C_{1-3} alkyl,

R5 is H

R_4 is a group chosen among:

- NR_8R_9, where R_8 is H or C_{1-3} alkyl and

R_9 is a methanesulfonyl, tosyl, tetrahydropyranyl, tetrahydrothiopyranyl possibly mono or di-substituted by oxygen on the S atom, piperidyl possibly substituted on the N-atom by a C_{1-3} alkyl, C1-3 acyl, aminosulfonyl, methanesulfonyl; or a group $(CH2)g-R_{10}$ where g is 1,2,3 and R_{10} is chosen among morpholine, furan, CN;

or R_8 and R_9 together with the N atom to which they are linked form a piperazine possibly substituted on one of its nitrogen by C_{1-3} alkyl, C1-3 acyl or methanesulfonyl;

- $N(R_{11})CO(CH_2)h-R_{12}$ where R_{11} is H, C_{1-3} alkyl; h is 0,1,2,3; and R_{12} is chosen among: morpholine, pyrrolidine possibly substituted with an hydroxy or an hydroxymethyl, piperidine possibly substituted with a group hydroxy, carboxyamido or aminosulfonyl, piperazine possibly substituted on the N-atom by C_{1-3} alkyl, triazole, tetrazole, 5-mercapto-tetrazole, furan, thiophene, thiomorpholine possibly mono or di-oxygenated on the S-atom, amino-cyclohexane possibly substituted by an hydroxy group.

$-COR_{13}$ wherein R_{13} is morpholine or piperazine possibly substituted with a C_{2-6}alkyl containing one or more ether or hydroxy groups.

Since compounds of formula (I) present various chiral centers the present invention obviously refers also to the single enantiomers and to the diastereoisomers mixtures.

State of the art

The NK2 receptor of tachykinins is widely present in the peripheral nervous system in mammals. One of the various effects of the selective stimulation of the NK2 receptor is the contraction of smooth muscles. Therefore the antagonists of the NK2 receptor are agents capable of controlling the excessive contraction of smooth muscles in all those pathologic condition where the release of tachykinins contributes to the genesis of the corresponding pathological disorder.

More particularly the broncospastic component of asthma, cough, pulmonary irritations, intestinal spasms or local spasms in bladder and ureter in the case of cystitis, infections and kidney colics can be considered conditions where the administration of NK2 antagonists is appropriated (E.M. Kudlacz et al. Eur. J.

X_1, X_2, X_3, X_4, same or different are a group -CONR- and -NRCO-,

R is H or methyl

R_1 and R_2 same or different, are::

-(CH_2)-Ar wherein Ar is an aromatic group chosen among benzene, pyridine, indole, possibly substituted up to two residues with substituents chosen among: C_{1-3} alkyl and haloalkyl, C_{1-3} alkyloxy, C_{2-4} amino alkyloxy, halogens, OH, NH_2, CN, NR_6R_7, where R_6 and R_7, same or different, are H or C_{1-3} alkyl;

R_3 is a group chosen among:

- CH_2-Ar_1 wherein Ar_1 is an aromatic group chosen among: alfa naphthyl, beta naphthyl, phenyl, phenyl substituted up to two residues chosen among C_{1-3} alkyl and haloalkyl, C_{1-3} alkyloxy, halogens, OH, NH_2,

R5 is H

R_4 is a group chosen among:

- NR_8R_9, where R_8 is H or C_{1-3} alkyl and

R_9 is chosen among: methanesulfonyl, tosyl, tetrahydropyranyl, tetrahydrothiopyranyl possibly mono or di-substituted by oxygen on the S atom, piperidyl possibly substituted on the N-atom by a C_{1-3} alkyl, C1-3 acyl, aminosulfonyl, methanesulfonyl; or a group (CH2)g-R_{10} where g is 1,2,3 and R_{10} is chosen among morpholine, furan, CN;

or R_8 and R_9 together with the N atom to which they are linked form a piperazine possibly substituted on the N atom with a C1-3alkyl, C1-3 acyl or methanesulfonyl;

- $N(R_{11})CO(CH_2)_h$-R_{12} where R_{11} is H, C_{1-3} alkyl; h is 0,1,2,3; and R_{12} is chosen among: morpholine, pyrrolidine possibly substituted with an hydroxy or hydroxymethyl, piperidine possibly substituted with a group hydroxy, carboxyamido or aminosulfonyl, piperazine possibly substituted on the N-atom by C_{1-3} alkyl, triazole, tetrazole, 5-mercapto-tetrazole, furan, thiophene, thiomorpholine possibly mono or di-oxygenated on the S-atom, amino- cylohexane possibly substituted by an hydroxy group.

- COR_{13} wherein R_{13} is a group chosen among morpholine and piperazine possibly substituted by a C_{2-6} alkyl containing one or more eth r or hydroxy

groups.

More preferred are the compounds of formula (I) wherein:

- X_1, X_2, X_3, X_4 are -CONR-,
- R is H;
- R1 is the lateral chain of triptophane;
- R2 is the lateral chain of phenylalanine possibly substituted with up to two residues chosen among: chlorine, fluorine, CF_3, OH, CN ; or a group 3-pyridyl-methyl, 4-pyridyl-methyl;
- R3 is benzyl.

and the other substituents re as above defined.

An even preferred group of compounds according to the invention are those wherein R, R1, R2, R3, R5, f, m are as above defined and:

R4 is a group NR8R9 wherein:

R8 is H or methyl;

R9 is a group chosen among: : 4-tetrahydropyranyl, 4-tetraidrothiopyranyl, 1-oxo-tetraidrothiopyran-4-yl, 1,1-dioxo-tetrahydrothiopyran-4-yl, N-methyl-4-piperidinyl, N-methansulfonyl-4-piperidinyl, N-aminosulfonyl-4-piperidinyl,

or R8 and R9 together with the N atom to which they are linked represent: N-methyl-piperazinyl, N-acetyl-piperazinyl, piperazinyl, N-methanesulfonyl-piperazinyl.

Among this last group of compounds the following are especially preferred:

i) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

ii) cyclo{Suc[1-(S)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

iii) cyclo{Suc[1-(R)-(1-methyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

iv) cyclo{Suc[1-(R)-(4-tetrahydrothiopyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

v) cyclo{Suc[1-(R)-(1-oxo-tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

Among the compounds of formula (I) wherein R, R1, R2, R3, R5, f, m are as hereabove defined preferred are also those wherein:

R_4 represents a group NR_8R_9, where R_8 is H and R9 is chosen among: methanesulfonyl, tosyl, a group $(CH2)g\text{-}R_{10}$ wherein g is 1, 2 and R_{10} is chosen among: morpholine, furan, CN.

Among this last group of compounds particularly preferred are:

xxi) cyclo{Suc[1-(S)-4-methanesulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxii) cyclo{Suc[1-(R)-4-methanesulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxiii) cyclo{Suc[1-(S)- (4-methylphenyl)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxiv) cyclo{Suc[1-(R)- (4-methylphenyl)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxv) cyclo{Suc[1-(S)-2-(4-morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxvi) cyclo{Suc[1-(R)-2-(4- morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxvii) cyclo{Suc[1-(R)-(2-furyl)methylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxviii) cyclo{Suc[1-(R)-cianomethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

Another preferred selection of the compound of formula (I) wherein R, R1, R2, R3, R5, f, m are as previously defined, those wherein:

R4 represents a group $-N(R_{11})CO(CH_2)h\text{-}R_{12}$ wherein R_{11} is H, h is 0 or 1, and R12 is chosen among. : 1-tetrazolyl, 5-mercapto-tetrazol-1-yl, 1-triazolyl, furanyl, thiophenyl, morpholine, 4-hydroxy-piperidine, 4-carboxyamido-piperidine, 3-hydroxy-pyrrolidine, 2-hydroxymethylpyrrolidine, 4-methyl-piperazine, 4-aminosulfonyl-piperazine, 1-oxo-thiomorpholine, 4-hydroxy-cyclohexan-1-yl-amino

Among the compounds of this last group particularly preferred are:

xliv) cyclo{Suc[1-(R)-2-(4-aminosulfonyl-piperazin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xlv) cyclo{Suc[1-(R)-2-(1-oxo-thiomorpholin-4-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xlvi) cyclo{Suc[1-(R)-2-(*trans*--4-hydroxy-cyclohexan-1-yl-amino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

Another preferred selection of compounds of formula (I) wherein R, R1, R2, R3, R5, f, m are as above defined are those wherein:

R4 is a group COR_{13} wherein R_{13} is a group chosen among: morpholine and 4-(hydroxyethyloxyethyl)-piperazine.

Among this last group of compounds especially preferred are:

xlvii) cyclo{Suc[1-(4- morpholine)carbonyl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xlviii) cyclo{Suc[1-(4-hydroxyethyloxyethyl-piperazin-1-yl)carbonyl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

Phamaceutically acceptable salts of compounds of formula (I) are for example the salts with inorganic acids (as hydrochloric, hydrobromic, hydroiodic, sulphuric, nitric, phosphoric) or organic acids (as acetic, propionic, succinic, malonic, citric, tartaric, methanesulfonic, p-toluensulfonic).

According to the invention the compounds of formula (I) containing peptide or pseudopeptide bonds can be obtained by the normal condensation reactions according to known techniques. A general method of preparation of peptide compounds (X_1-X_4 = -CONR-, -NRCO-) is for example to synthetise in a solution the linear peptide chain using the appropriate aminoacids, carboxylic or diamino derivatives suitably protected, and after selective de-protection of the terminal C- and N- chains, to cyclise in polar organic solvents in a diluted solution. For the activation of the carboxylic group normally the methods using EDCI.HCl and HOBt or PyBOP and DIEA in DMF are preferred.

The dicarboxylic precursors containing the R_4 group and the diamino precursors containing the R_3 group were prepared according to the methods described in literature.

In particular in the synhesis of derivatives wherein R_4 = amino or carboxylic group, suitably protected aspartic or carbosuccinic acid were used respectively (E. Perrotta et al, Synlett, 1999, 144-146). The synthesis of the ethylendiamine derivatives containing the R_3 groups was performed according to G. Kokotos et al., J. Chem. Research (S), 1992, 391.

The compounds of formula (I) as above described are powerful antagonists of NK2 receptor of tachykinins and can be administered as agents capable of controlling the excessive smooth muscular contraction in whatever pathological condition where the release of tachykinins contributes to the pathology.

In particular the broncospastic component of asthma, cough, pulmonary irritation, the intestinal spasms or local spasms of bladder and ureter during cystitis, infections and kidneys colics, can be considered conditions where the administration of compounds of formula (I) as NK2 antagonists, can be appropriate.

The compounds of formula (I) object of the present invention are useful for the administration to superior animals and humans by parenteral, oral, by inhalation, sublingual administration giving pharmacological effects thanks to their properties.

For the parenteral administration (intravenous, intramuscular and intradermal) sterile solutions or lyophilised preparations are used.

For nasal, by inhalation or sublingual administration aqueous solutions, aerosol, powders or capsules are used as appropriate.

The quantity of active principle administerd with the above said formulations is normally comprised between 0.1 and 10 mg/kg of patient body weight.

Hereinafter some specific examples of compounds according to the invention are reported.

EXAMPLE 1: cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein X_1 = X_2 = X3 = X_4 = -CO-NH-; R_1 = -CH_2-(indol-3-yl); R_2 = R_3 = -CH_2-C_6H_5; R4 = (4-tetrahydropyranyl)amino; R_5 = H; m = 0, f = 1; the carbon atoms C-R_1 and C-R_2 have configuration S, while C-R_3 and C-R_4 have configuration R).

As starting compound the cyclo{-Suc[1-(R)-amino]-Trp-Phe-[(R)-NH-

$CH(CH_2C_6H_5)$-CH_2-NH]-} (Compound A).

(compound of formula (I) wherein: $X_1 = X_2 = X3 = X_4$ = -CO-NH-; R_1 = -CH_2-(indol-3-yl); $R_2 = R_3$ = -CH_2-C_6H_5; R_4 = -NH_2; R_5 = H; m = 0, f = 1; the carbon atoms C-R_1 and C-R_2 have configuration S, while C-R_3 and C-R_4 have configuration R) is used . The compound A is prepared as follow:

a) Synthesis of dipeptide Boc-Trp-Phe-OH

To a solution of H-Trp-Phe-OH (5 g,) in dioxane (30 ml), H_2O (15 ml) and NaOH 1M (15.6 ml), cooled at 0-5°C, under stirring, of-tert-butyldicarbonate (3.4 g) was added. The reaction mixture was left under stirring for 2 h, concentrated, and extracted with pentane (2 x 20 ml). The aqueous phase was cooled with ice, added wit AcOET (50 ml), acidified with $KHSO_4$ up to pH 2-3, separated and extracted with AcOEt (2 x 50 ml). The organic phases pooled together were washed with brine (50 ml), dried and evaporated under vacuum at 30°C, giving 6 g of the desired compound as a white semisolid residue.

TLC: Rf 0.55 (chloroform/cyclohexane/AcOH/H_2O = 45/45/5/5), 0.52 ($CHCl_3$/ MeOH = 9/1)

b) Synthesis of (R)-1-benzyl-2-(N-benzyloxycarbonylamino)ethylamina

(R)-1-benzyl-1-(N-*tert*-butyloxycarbonylamino)ethylamina, prepared as described in G. Kokotos et al., J. Chem. Research (S), 1992, 391, was transformed into the corresponding (R)-benzyl-1-(N-*tert*-butyloxycarbonylamino)-2-(benzyloxycarbonylamino)ethylamina and this into (R)-1-benzyl-2-(N-benzyloxycarbonylamino)ethylamina according to the usual methods of protection and deprotection of aminoacids.

c) Synthesis of Boc-Trp-Phe-[(R)-NH-CH(CH2-C_6H_5)-CH_2-NH-Z]

To a solution of Boc-Trp-Phe-OH (1.19 g, 2.63 mmoli) in anhydrous DMF (10 ml) (R)-1-benzyl-2-(benzyloxycarbonylamino)ethylamine (750 mg), PyBOP (1.37 g) e DIEA (0.9 ml) were added under nitrogen. The reaction mixture was left under stirring for a night at room, added with AcOEt (80 ml), washed with HCl 1N (3 x 30 ml), Na_2CO_3 5% (3 x 30 ml) and H_2O (30 ml). The organic phase was evaporated under vacuum at 30°C, giving 1.8 g of ivory colored solid residue.

The crude was purified by washing in a warm AcOEt suspension followed by

The compound is prepared according to Example 1 but using as reagent (1-aminosulfonyl)piperidin-4-one.

HPLC (Method A2): rt =13.5 min.

MS: m/z = 743.2 (MH^+).

EXAMPLE SEMPIO 17: cyclo{Suc[1-(R)-(piperazin-1-yl)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of formula I wherein R4 = piperazin-1-yl and the other substituents are as in Compound A.

The compound is prepared according to Example 1 but using as reagent N-Boc iminodiacetaldheyde, carrying on the reaction for 16 h and removing the protective group N-Boc with TFA in dichloromethane. The so obtained product is purified by preparative HPLC (Method P2).

1H-NMR (DMSO-d6, 500 MHz): d 2.39 (1H, dd, J = 10.2, 12.4 Hz); 2.65-2.79 (5H, m); 2.79-2.91 (3H, m); 2.99-3.15 (6H, m); 3.22-3.48 (m, overlapping the water signal); 3.51 (1H, dd, J = 4.4, 10.1 Hz); 3.95-4.04 (1H, m); 4.08-4.18 (2H, m); 6.92 (1H, d, J = 8.7 Hz); 6.98 (1H, m); 7.04-7.11 (2H, m); 7.11-7.28 (10H, m); 7.33 (1H, d, J = 8.1 Hz); 7.32-7.37 (1H, m); 7.44 (1H, d, J = 7.9 Hz); 8.32 (1H, d, J = 7.4 Hz); 8.40 (1H, bs); 8.71 (1H, d, J = 5.0 Hz); 10.82 (1H, d, J = 2.1 Hz).

MS: m/z = 650, MH^+.

EXAMPLE 18: cyclo{Suc[1-(R)-4-methyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of formula I wherein R4 = 4-methyl-piperazin-1-yl and the other substituents are as described in Compound A)

To 50 mg of the compound described in example 17, solved in 2 ml methanol, 10 mg paraformaldeide, 25 mg of sodium cianoborohydride, and 50 µl actic acid are added. The solution is stirred for one night, thereafter the solvent is evaporated, the residue is treated with HCl 0.1N, potassium carbonate up to basic pH and extracted with ethyle acetate, washed with brine and dried on magnesium sulfate. The solvent is evaporated giving 34 mg of crude product which are purified by preparativeHPLC (Method P3).

MS: m/z = 664.5 (MH^+).

The compound was prepared according to EXAMPLE 29 but using as reagent 2-(1-oxo-thiomorpholin-4-yl)acetic acid.

HPLC (Method A2): rt =11.7 min.

MS: m/z = 740.4 (MH^+)

EXAMPLE 46: cyclo{Suc[1-(R)-2-*(trans*-4-hydroxy-cyclohexan-1-yl-amino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is 2-*(trans*-4-hydroxy-cyclohexan-1-yl-amino)acetylamino and the other substituents are as described for Compound A).

The compound was prepared according to EXAMPLE 29 but using as reagent 2-*(trans*-4-hyroxy-cyclohexan-1-yl-amino)acetic acid.

HPLC (Method A2): rt =11.6 min.

MS: m/z = 736.3 (MH^+)

EXAMPLE 47: cyclo{Suc[1-(4-morpholino)carbonyl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein : X_1 = X_2 = X3 = X_4 = -CO-NH-; R_1 = -CH_2-(indol-3-yl); R_2 = R_3 = -CH_2-C_6H_5; R4 = (4-morpholino)carbonyl; R_5 = H; m = 0, f = 1; the C-R_1 and C-R_2 carbon atoms have S-configuration, while C-R_3 has R-configuration)

a) Synthesis of Boc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH_2]

To a solution of Boc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-Z] (1.20 g) in methanol (36 ml) and DMF (14 ml), Pd/C 10% (120 mg) was added. The mixture was stirred and hydrogenated at room temperature and pressure for 2 h. The mixture was filtered and the solid washed with methanol.The leuated were pooled together and evaporated giving a viscous oil which was solubilised in ethylacetate. The resulting solution was washed with water and brine and dried on anhydrous sodium sulfate. By evaporating the organic phase 870 mg of a white solid were obtained.

HPLC (Method A3): rt =11.8 min.

MS (ES+): [MH+] = 584

b) Synthesis of Boc-Trp-Phe-{(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-[2-(4-nitro-

hydroxybenzotriazole; rt = retention time; THF = tetrahydrofuran. The numbering of the substituents on the succinic group indicated as -Suc(1-NH_2)- is realised with R_4 = NH2, R5 = H and X_3 and X_4 = CONR.

Biological Activity

The compounds described in the present invention act as antagonists on the NK2 receptor of tachykinins

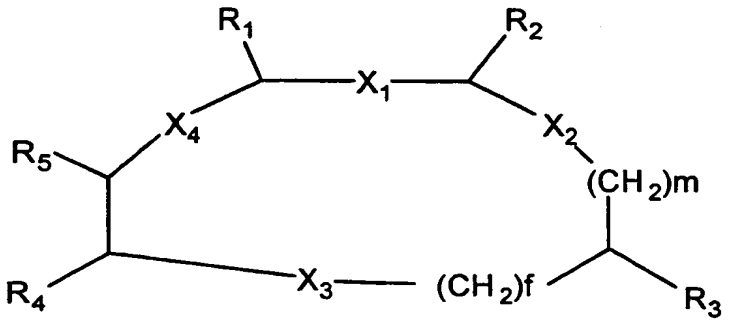
The biological activity was tested in three different functional tests in vitro using rabbit pulmonary arteria (RPA), hamster trachea (HT) and rat urinary bladder (RUB) according to the methods described by Maggi C.A. et al. Br. J. Pharmacol. 1990, 100, 588, D'Orleans-Juste P. et al. Eur. J. Pharmacol. 1986, 125, 37 e Maggi C.A. et al. J. Pharmacol. Exp. Ther. 246, 308, 1988. The affinity of the compounds for the human NK2 receptor was evaluated in a test of binding using membranes of CHO (Chinese hamster ovary) cells transfected with the NK-2 receptor of human ileum and the radioligand [^{125}I]NKA (Amersham, specific activity 2000 Ci/mmol) at the concentration of 100 pM in studies of competition. The examined compounds were tested in a range of concentration comprised between 0.01 nM and 10mM. After incubation (30 min., 20°C) the samples were filtered and the radioactivity was determined using a gama-counter.

The data collected by functional studies are expressed as pA_2 (Arunlakshana O. and Schild H.O., Br. J. Pharmacol. Chemother. 1959, 14, 45) and those deriving from studies of binding are expressed as pKi (-log Ki calcolated with the program LIGAND: Munson P.J. et al. Anal. Biochem. 1980, 107, 220).

The compounds of the invention showed good activity in all the above said tests with values of pA_2 up to 9.5 and values of pKi up to 10.6

CLAIMS

1. Monocyclic compounds of general formula (I)



(I)

wherein:

X_1, X_2, X_3, X_4, same or different, are a group chosen among: -CONR-, -NRCO-, $-CH_2-NR-$, $-NR-CH_2-$ where R is H , C_{1-3} alkyl, benzyl;

f, m, same or different, are a number chosen among 0,1 and 2;

R_1 and R_2, same or different, represent a group:

$-(CH_2)_r$ -Ar where r = 0, 1, 2 and Ar is an aromatic group chosen among: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, benzoimidazole, possibly substituted with up to 2 substituents chosen among C_{1-3} alkyl, haloalkyl, C_{1-3} alkyoxy, C_{2-4} amino-alkyoxy, halogens, OH, NH_2, CN, NR_6R_7, where R_6 ed R_7, same or different, are H or C_{1-3} alkyl,

R_3 is a group chosen among the following gropus:

$(CH_2)_r$-Ar_1 where r = 0, 1, 2 and Ar_1 is an aromatic group chosen among: benzene, naphtalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, benzoimidazole,

possibly substituted with up to 2 groups chosen among C_{1-3} alkyl and haloalkyl, C_{1-3} alkyoxy and amino-alkyoxy, halogens, OH, NH_2, NR_6R_7, where R_6 and R_7, same or different, are H or C_{1-3} alkyl,

R5 is H

R_4 is a group chosen among:

- NR_8R_9, where R_8 is H or C_{1-3} alkyl and

R_9 is a methanesulfonyl, tosyl, tetrahydropyranyl, tetrahydrothiopyranyl possibly

mono or di-substituted by oxygen on the S atom, piperidyl possibly substituted on the N-atom by a C_{1-3} alkyl, C1-3 acyl, aminosulfonyl, methanesulfonyl; or a group $(CH2)g-R_{10}$ where g is 1,2,3 and R_{10} is chosen among morpholine, furan, CN;

or R_8 and R_9 together with the N atom to which they are linked form a piperazine possibly substituted on one of its nitrogen by a C_{1-3} alkyl, C1-3 acyl o methanesulfonyl;

$N(R_{11})CO(CH_2)h-R_{12}$ where R_{11} is H, C_{1-3} alkyl; h is 0,1,2,3; and R_{12} is chosen among: morpholine, pyrrolidine possibly substituted with an hydroxy or hydroxymethyl, piperidine possibly substituted with a group hydroxy carboxyamido or aminosulfonyl, piperazine possibly substituted on the N-atom by C_{1-3} alkyl, triazole, tetrazole, 5-mercapto-tetrazole, furan, thiophene, thiomorpholine possibly mono or di-oxygenated on the S-atom, amino- cyclohexane possibly substituted by an hydroxy group.

- COR_{13} wherein R_{13} is a group chosen among morpholine and piperazine possibly substituted by a C_{2-6} alkyl containing oneor more ether or hydroxy groups;

as enantiomers or mixture of diastereoisomers, and their pharmaceutically accepatble salts.

2. Compound according to Claim 1 wherein:

f is 1

m is 0

X_1, X_2, X_3, X_4, same or different are a group -CONR- and -NRCO-,

R is H or methyl

R_1 and R_2 same or different, are:

$-CH_2$-Ar wherein Ar is an aromatic group chosen among benzene, piridine, indole, possibly substituted up to two residues with substituents chosen among: C_{1-3} alkyl and haloalkyl, C_{1-3} alkyloxy, C_{2-4} amino alkyloxy, halogens, OH, NH_2, CN, NR_6R_7, where R_6 and R_7, same or different, are H or C_{1-3} alkyl;

R_3 is a group chosen among:

- CH_2-Ar_1 wherein Ar_1 is an aromatic group chosen among: alfa naphthyl, beta naphthyl, phenyl, phenyl substituted up to two residues chosen among C_{1-3} alkyl and haloalkyl, C_{1-3} alkyloxy, halogens, OH, NH_2,

R5 is H

R_4 is as defined in Claim 1.

3. Compounds according to Claim 2 wherein:

- X_1, X_2, X_3, X_4 are -CONR-,

R is H

- R1 is the lateral chain of tryptophan;

- R2 is the lateral chain of phenylalanine possibly substituted with up to two residues chosen among: chlorine, fluorine, CF_3, OH, CN; or a group 3-pyridyl-methyl; or a group 4-pyridyl-methyl;

- R3 is benzyl.

and f, m, R_4 and R_5 are as defined in claim 2

4.Compounds according to claim 3 wherein:

R, R1, R2, R3, R5, f, m are as above defined and:

R4 is a group NR8R9 wherein:

R8 is H or methyl;

R9 is a group chosen among: : 4-tetrahydropyranyl, 4-tetrahydrothiopyranyl, 1-oxo-tetrahydrothiopyran-4-yl, 1,1-dioxo-tetrahydrothiopyran-4-yl, N-methyl-4-piperidinyl, N-metansulfonyl-4-piperidinyl, N-aminosulfonyl-4-piperidinyl,

or R8 and R9 together with the N atom to which they are linked represent: N-methyl-piperaziniyl, N-acetyl-piperazinyl, piperazinyl, N-methanesulfonyl-piperazinyl

5. Compounds according to Claim 4 represented by:

i) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

ii) cyclo{Suc[1-(S)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

iii) cyclo{Suc[1-(R)-(1-methyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

iv) cyclo{Suc[1-(R)-(4-tetrahydrothiopyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

v) cyclo{Suc[1-(R)-(1-oxo-tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

vi) cyclo{Suc[1-(R)-(1,1-dioxo-tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

vii) cyclo{Suc[1-(R)-N-methyl-N-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

viii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Tyr-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

ix) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-F)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

x) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(3,5-F)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xi) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-CN)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-CF3)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xiii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Ala(4-pyridyl)-[R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xiv) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Ala(3-pyridyl)-[R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xv) cyclo{Suc[1-(R)-(1-methylsulfonyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xvi) cyclo{Suc[1-(R)-(1-aminosulfonyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xvii) cyclo{Suc[1-(R)-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xviii) cyclo{Suc[1-(R)-4-methyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xix) cyclo{Suc[1-(R)-4-acetyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-

$CH_2NH]\}$

xx) cyclo{Suc[1-(R)-4-methanesulfonyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-$CH_2NH]\}$

6. Compound according to Claim 3 wherein :

R_4 represents a group NR_8R_9, where R_8 is H and R9 is chosen among: methanesulfonyl, tosyl, a group (CH2)g-R_{10} wherein g is 1, 2 and R_{10} is chosen among: morpholine, furan, CN.

and f, m, X_1, X_2, X_3, X_4, R, R_1, R_2, R_3 and R_5 are as defined in claim 3

7. Compound according to claim 6 represented by:

xxi) cyclo{Suc[1-(S)-4-methanesulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-$CH_2NH]\}$

xxii) cyclo{Suc[1-(R)-4-methanesulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-$CH_2NH]\}$

xxiii) cyclo{Suc[1-(S)-(4-methylphenyl)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-$CH_2NH]\}$

xxiv) cyclo{Suc[1-(R)-(4-methylphenyl)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-$CH_2NH]\}$

xxv) cyclo{Suc[1-(S)-2-(4-morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-$CH_2NH]\}$

xxvi) cyclo{Suc[1-(R)-2-(4-morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-$CH_2NH]\}$

xxvii) cyclo{Suc[1-(R)-(2-furyl)methylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-$CH_2NH]\}$

xxviii) cyclo{Suc[1-(R)-cianomethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-$CH_2NH]\}$

8. Compounds according to claim 3 wherein:

R4 is a group - $N(R_{11})CO(CH_2)_h$-R_{12} wherein R_{11} is H, h is 0 or 1, and R12 is chosen among. : 1-tetrazolyl, 5-mercapto-tetrazol-1-yl, 1-triazolyl, furanyl, thiophenyl, morpholine, 4-hydroxy-piperidine, 4-carboxyamido-piperidine, 3-hydroxy-pyrrolidine, 2-hydroxymethylpyrrolidine, 4-methyl-piperazine, 4-

aminosulfonyl-piperazine, 1-oxo-thiomorpholine, 4-hydroxy-cyclohexan-1-yl-amino and f, m, X_1, X_2, X_3, X_4, R, R_1, R_2, R_3 and R_5 are as defined in claim 3.

9. Compounds according to Claim 8 represented by:

xxix) cyclo{Suc[1-(R)-2-(4-morpholino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxx) cyclo{Suc[1-(S)-2-(4-morpholino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxi) cyclo{Suc[1-(S)-2-(tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxii) cyclo{Suc[1-(R)-2-(tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxiii) cyclo{Suc[1-(S)-2-(5-mercapto-tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxiv) cyclo{Suc[1-(R)-2-([1,2,4]triazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxv) cyclo{Suc[1-(R)-2-(furanil)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxvi) cyclo{Suc[1-(R)-2-(thiophen-3-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxvii) cyclo{Suc[1-(R)-(4-morpholino)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxviii) cyclo{Suc[1-(R)-2-(4-hydroxy-piperidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxix) cyclo{Suc[1-(R)-2-(4-aminocarbonyl-piperidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xl) cyclo{Suc[1-(R)-2-(3-hydroxy-pyrrolidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xli) cyclo{Suc[1-(R)-2-(2-(S)-hydroxymethyl-pyrrolidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xlii) cyclo{Suc[1-(R)-2-(4-methyl-piperazin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-

$CH(CH_2\text{-}C_6H_5)\text{-}CH_2NH]\}$

xliii) cyclo{Suc[1-(R)-2-(4-methyl-piperazin-1-yl)carbonylamino]-Trp-Phe-[(R)-NH-$CH(CH_2\text{-}C_6H_5)\text{-}CH_2NH]\}$

xliv) cyclo{Suc[1-(R)-2-(4-aminosulfonyl-piperazin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-$CH(CH_2\text{-}C_6H_5)\text{-}CH_2NH]\}$

xlv) cyclo{Suc[1-(R)-2-(1-oxo-thiomorpholin-4-yl)acetylamino]-Trp-Phe-[(R)-NH-$CH(CH_2\text{-}C_6H_5)\text{-}CH_2NH]\}$

xlvi) cyclo{Suc[1-(R)-2-*(trans*-4-hydroxy-cyclohexan-1-yl-amino)acetylamino]-Trp-Phe-[(R)-NH-$CH(CH_2\text{-}C_6H_5)\text{-}CH_2NH]\}$

10. Compounds according to Claim 3 wherein:

R4 represents a group COR_{13} wherein R_{13} is a group chosen among morpholine and 4-(hydroxyethyloxyethyl)-piperazine.

and f, m, X_1, X_2, X_3, X_4, R, R_1, R_2, R_3 and R_5 are as defined in claim 3

11. Compounds according to claim 10 represented by:

xlvii) cyclo{Suc[1-(4-morpholino)carbonyl]-Trp-Phe-[(R)-NH-$CH(CH_2\text{-}C_6H_5)\text{-}CH_2NH]\}$

xlviii) cyclo{Suc[1-(4-hydroxyethyloxyethyl-piperazin-1-yl)carbonyl]-Trp-Phe-[(R)-NH-$CH(CH_2\text{-}C_6H_5)\text{-}CH_2NH]\}$

12. Pharmaceutical compositions containing as active principle compounds of general formula (I) according to Claim 1 in combination with pharmaceutically acceptable carriers or excipients.

13. Pharmaceutical compositions according to Claim 12 for use as tachykinins antagonists.

14. Pharmaceutical compositions according to claim 13 for use as antagonists on human NK2 receptor .

15. Pharmaceutical compositions according to claim 14 for use in the treatment of the broncospastic component of asthma, cough, pulmonary irritation, intestinal spasms or local spasms of bladder, uretere during cystitis, infections, kidney colics.

16. Use of a compound according to Claim 1 as tachykinins antagonist

17. Use of a comound according to Claim 1 as NK-2 antagonist.

18. Use of a compound according to Claim 1 for the treatment of the broncospastic component of asthma, cough, pulmonary irritation, intestinal spasms or local spasms of bladder, uretere during cystitis, infections, kidney colics.

19.Method for the treatment of the broncospastic component of asthma, cough, pulmonary irritation, intestinal spasms or local spasms of bladder, uretere during cystitis, infections kidney colics wherein amounts of 0,1 - 10mg/ body weight of an active principle represented by compounds of formula (I) according to Claim 1 are administered to the patient.

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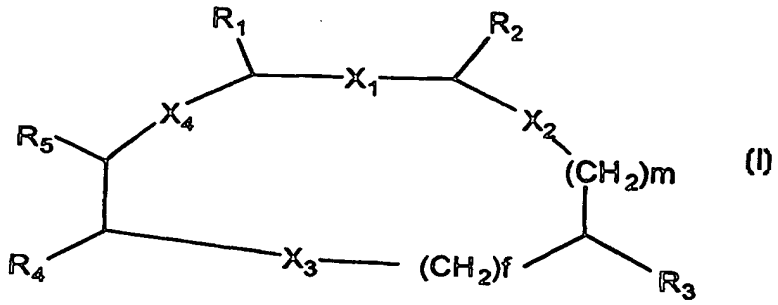

(57) Abstract

Compounds of formula (I) and their pharmaceutically acceptable salts having antagonist action on the NK2 receptor are described. Processes for the preparation of the above said compounds and pharmaceutical preparations containing them are also described.

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